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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,549	04/01/2002	Michio Kubota	KUBOTA=9	3265

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,549	KUBOTA ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,8-15 and 43-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,8-15 and 43-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-4, 8-15, 43-46 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 5-4-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn few of the rejections under 35 U.S.C. 112, 2nd paragraph in view of claim cancellations and claim amendments. Examiner has also withdrawn the rejection under 35 U.S.C. 112, Ist paragraph for lack of biological deposit certification in view of the certification now provided by the applicant.

Amendments to specification

All papers filed on 5-4-04requesting amendments to specification have not been entered. This is because applicant has failed to provide a marked-up version of the large number of amendments to the specification. They are placed in the file but not entered. Applicant is urged to file a marked-up version in order to be considered and entered.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless

the references have been cited by the examiner on form PTO-892, they have not been considered.

In response to the above, applicant has drawn the attention of the Examiner to the IDS filed July 2, 2002. However, Examiner could not find such an IDS in the application and is in the process of retrieving the application to find out whether such an IDS exists in the application. Examiner requests applicant to find out whether an acknowledgement acknowledging the receipt of the IDS was received from the Office.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 3-4, 8-15, 43-46 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1, 4, 44 recite the phrase "substantially increasing the reducing power". The metes and bounds of the above phrase are not clear to the Examiner. A perusal of the specification did not provide the Examiner with a specific definition for the above phrase rendering the claims indefinite.

In response to the previous Office action, applicant has traversed the above rejection arguing that the term is often used in conjunction with another term to describe a particular characteristic of the claimed invention and that the term is broad but not indefinite. Applicant has referred to a court decision. Examiner respectfully disagrees with such an argument. While the term may not have been indefinite in case of the claim the court considered, in the context

of the instant claim, the phrase continues to be indefinite because the metes an bounds are not clear to the examiner. What is again not clear to the Examiner is the scope of the broad term. There is not definition in the specification for the phrase and it is also not clear as to whose of which component's reducing power, applicant is claiming, whether it is that for the enzyme or that of the oligosaccharide product formed? Therefore, the above rejection is maintained.

Claim 1 and claims 3-4, 8-15, 43, 46 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the phrase "and having an amino acid sequence of SEQ ID NO:1, 11 or 18 and a molecular weight of about 94,000....". This phrase is highly unclear to the Examiner. The phrase "having an amino acid sequence" in the above phrase is considered in the Patent Office as being equivalent to "consisting of". That said, the amino acid sequences SEQ ID NO:1, 11 or 18 are all small peptide fragments of 6-8 amino acids, not full length sequences whose molecular weights would fall in the molecular weight range claimed in the claims. However, combining the above interpretations, it will have to be concluded from he claim as written, that the amino acid sequences SEQ ID NO:1, 11, or 18 have a molecular weight varying between 94,000 to 140,000, which is physically or chemically impossible. This renders the claim indefinite. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter (new matter) which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1, 4, 44 and claims 2, 8-15, 43, 45-46 which depend therefrom are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1, 4, 44 are drawn to isomaltosylglucosaccharide synthase polypeptides having various characteristics such as molecular weight, temperature optimum, pH ranges etc., none of which match with the characteristics described in the specification. For example, in claim 4, the enzyme claimed has a molecular weight of 140,000 and an isoelectric point of 4.7 to 7.8. Applicant indicates that said amendment has support in example 5 on p69. A perusal of said page indicates that the molecular weight of the enzyme does not match with the isoelectric point of the enzyme. Similarly, the enzyme now claimed in claim 44 appears to be in example 16-1 based on the molecular weight. However, the isoelectric points and other characteristics do not match. Similarly Examiner could not find matching support for other characteristics such as incapable of forming dextran, inhibited by EDTA or stabilized by Ca^{2+} and Mn^{2+} etc. Such characteristics claimed now constitutes a "new matter". Therefore claims 1, 4, 44 are rejected for introducing "new matter" into the claims.

Claims 1, 3, 8, 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isomaltosylglucosaccharide-forming enzyme (IMG) isolated from *Bacillus* sp., or *Arthrobacter sp.*, wherein said enzyme comprises either SEQ ID NO:1, 11 or 18, and wherein said enzyme forms a saccharide having a glucose polymerization degree of at least three with both, an α-1,6-glucosidic linkage (as a linkage at the non-reducing end) and the α 1,4-glucosidic linkage (other than the linkage at the non-reducing end) by catalyzing the α glucosyl transfer from a saccharide having glucose polymerization of at least two and having α 1,4-glucosidic linkage as a linkage at the non-reducing end, does not reasonably provide enablement for any such enzyme isolated from any or all sources including recombinant mutants and variants and having a broad molecular weight ranging from 94,000 to about 140,000 Daltons. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1, 3, 8, 12-15 are so broad as to encompass any IMG from any source including recombinants, mutants and variants and having a broad molecular weight ranging from 94,000 to about 140,000 Daltons. The scope of the claims is not commensurate with the enablement

provided by the disclosure with regard to the extremely large number of IMG's broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a single IMG isolated from *Bacillus* species or *Arthrobacter sp.*, wherein said enzyme comprises SEQ ID NO:1, 11, or 18 and wherein said enzyme forms a saccharide having a glucose polymerization degree of at least three with both, an α-1,6-glucosidic linkage (as a linkage at the non-reducing end) and the α 1,4-glucosidic linkage (other than the linkage at the non-reducing end) by catalyzing the α glucosyl transfer from a saccharide having glucose polymerization of at least two and having α 1,4-glucosidic linkage as a linkage at the non-reducing end. It would require undue experimentation of the skilled artisan to make and use the polypeptides as claimed by the applicants. The specification is limited to teaching the use of a polypeptide comprising SEQ ID NO:1, 11 or 18 isolated from specific sources such as bacillus or Arthrobacter, as an IMG, but provides no guidance with regard to the making of variants and mutants or with regard to methods of isolating it from any or all sources. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref:

U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any or all IMG isolated from any source including recombinants, mutants and variants and having a broad molecular weight ranging from 94,000 to about 140,000 Daltons because the specification does not establish: (A) a rational and predictable scheme for isolation of any IMG from any source having a broad molecular weight ranging from 94,000 to about 140,000 Daltons; (B)regions of the protein structure which may be modified without affecting IMG activity; (C) the general tolerance of IMG polypeptides to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any amino acid residue in a polypeptide comprising SEQ ID NO:1, 11 or 18 with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including IMGs from all or any sources or with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of IMGs having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicant has traversed the above rejection arguing argue that the rejection under 35 U.S.C. §112, first paragraph is not proper because Experiment 5-1 on pages 69-71, Experiment 8-1 on pages 81-83, Experiment 12-1 on pages 97-99 and Experiment on pages 112-114 provide enablement for the subject matter as recited in amended claim. Examiner respectfully disagrees with such an argument. This is because while the examples provide support for isolation of specific enzymes from specific microbial sources, it does not provide enablement for isolating said enzymes from any or all sources or for making any or all types of variants, mutants, or recombinants. Furthermore, while methods to produce variants of a known polypeptide sequence such as site-specific mutagenesis, random mutagenesis, etc. and methods of culturing are well known to the skilled artisan producing variants as claimed by applicants (without any indication of conservative and consensus sequences and amino acid residues that can be modified without altering the function of the polypeptide) requires that one of ordinary skill in the art know or be provided with guidance for culturing and isolation of said enzyme from all sources and as well as the selection

of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of isolating and testing or producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. Therefore the above rejection is maintained.

Claims 1, 3, 8, 12-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3, 8, 12-15 are directed to a genus of IMG comprising a specific 9-10 amino acid long peptide sequences (SEQ ID NO:1, 11, or 18). As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are

representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The specification fails to describe any other representative species by sufficient identifying characteristics (i.e., considerable amino acid sequence information) or properties to show that applicant was in possession of the claimed genus. The identifying characteristics recited in claims 1, 3, 8, 12-15 constitutes a minor aspect of the structural description-- does not include sufficient characteristics to limit the claimed genus to proteins which are not highly variable in both structure and function. The claims include species in which a large percent of the amino acid sequence (depending on the total number of amino acids in the polypeptide) of the single disclosed species has been substituted as well as allowing alterations in functional characteristics such as substrate specificity, temperature optima, pH optima, and inhibitor/activator profiles. Therefore, the species within the genus are highly variable in both structure and function. While claim 1 has characteristic to the limitations of the genus (i.e., having SEQ ID NO:1, 11or 18) this characteristic, by itself is not sufficient to change the fact that the claims include proteins which are highly variable in both structure and function. Thus for all the reasons discussed, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicant has traversed the above rejection arguing that the claims have now been amended to recite SEQ ID NO and therefore the claimed invention is amply described. Examiner respectfully disagrees with such an argument and amendment to be persuasive to overcome the above rejection. This is because, the SEQ ID NO provided refers to short fragment or peptide of the enzyme and does not represent the full length sequence. Hence the above rejection is maintained.

Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The examiner can normally be reached on 6.30 a.m. to 3.00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0939. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Manjunath N. Rao
July 20, 2004